REMARKS

I. Status of the Claims

Claims 69-88 are currently pending, with claims 76-78 withdrawn from consideration as directed to a non-elected invention. Upon entry of this amendment, claim 69 is amended and claims 73-74 canceled without prejudice or disclaimer. Claim 69 has simply been amended to recite specifically to vMCK-2, with compositions comprising mC10 introduced in new claims (see below). Claims 73-74 were canceled because they are redundant in view of the amendment to claim 69 and the introduction of the new claims. Applicants reserve the right to reintroduce the unamended or cancelled claims in this or another application.

New claims 89-106 are introduced upon entry of this amendment. All the new claims are within the same restriction group as the claims previously presented. All the new claims except claims 94-96 read on the elected species (i.e., mC10 and tumor antigens). Claims 69-106 are thus pending following entry of this amendment. The new claims are fully supported by the previously pending claims.

II. Claim Rejections under 35 U.S.C. §103

Claims 69-72, 74, 75 and 79-88 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Kedar, et al. (Advances in Cancer Research 59:245-322, 1992) in view of published PCT application WO 98/33520 to Bystryn , Mohamadzadeh et al. (Archives of Dermatological Research 289:435-439, 1997) and Orlofsky et al., (Cytokine 12:220-228, March 2000). Claims 69-73, 75 and 79-88 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Kedar in view of Bystryn and Saederup, et al. (PNAS 96:10881-10886, September 1999).

A. Currently Claimed Invention

Independent claims 69 and 89 are currently directed to compositions that comprise an antigen and either viral murine cytomegalovirus (vMCK-2 or simply MCK-2) (claim 69) or mC10 (or simply C10) (claim 89). These particular chemokines were shown

Amendments to the Drawings:

The attached drawing sheets includes a new set of formal drawings for Figs. 1 and 2. These drawings include changes to Fig. 1 and 2.

Sheet 1, which includes Fig. 1, replaces the original sheet including Fig. 1. An annotated sheet labeled Fig.1 is enclosed showing the changes made.

Sheet 2, which includes Fig. 2, replaces the original sheet including Fig. 2. The new sheet simply brings the original sheet into conformity with the formal requirements of 37 C.F.R. 1.84.

Attachment: Replacement Sheets for Figs. 1 and 2
Annotated Sheet Showing Changes for Fig. 1

through *in vivo* testing with murine and *primate* (rhesus monkey) model systems to cause unexpectedly high levels of infiltration of various antigen-presenting cells ("APCs"; e.g., dendritic cells and mononuclear cells) at the site of injection (see, e.g., Examples 2-6). The level of infiltration was considerably higher than for several other chemokines that were tested, some of which produced minimal if any response (see, e.g., Examples 2-5), and to significantly augment the immune response produced even when antigens were injected as part of a composition containing an adjuvant (see, e.g., Example 6). These discoveries are important with respect to a goal of the current invention because increased infiltration of APCs at the site of injection of the antigen would be expected to enhance the immune response to the injected antigen, especially the adaptive immune responses which are important in, for example, responses to cancer and viral, parasitic and yeast/fungal infections. The results with mC10 and vMCK-2 are also unexpected because they demonstrate that *murine* chemokines can nonetheless induce an immune response in *primates*. This activity is particularly surprising since there appears to be no human homolog of mC10 nor a homolog of vMCK-2 produced by a virus that infects humans.

B. Summary of Cited References

The Office Action states that Kedar discusses administering tumor antigens in combination with cytokines as part of an immunotherapy strategy, including incorporation of such combinations in liposomes to mitigate against degradation of the cytokine. Bystryn is said to discuss the administration of liposome compositions by oral, inhalation, intradermal, subcutaneous, intramuscular, intravenous and topical routes. Mohamadzadeh and Orolofsky are cited as discussing C10 as being involved in the initiation of inflammatory responses in murine cells. The Office Action cites Saederup as evidence that MCK-2 was known to recruit and activate monocytes or macrophages in murine cells.

The Office concludes that it would be obvious to use C10 in the liposome/cytokine compositions discussed in Kedar and Bystryn for use in inducing an immune response because Hohamadzadeh and Orolofsky discuss how C10, which as a chemokine is a member of the larger cytokine family, can initiate an immune response. Similarly, the Office

concludes that it would have been obvious to the skilled practitioner to use MCK-2, also a chemokine and thus a member of the much larger cytokine family, as discussed in Saederup in the liposome/cytokine compositions discussed in Kedar and Bystryn for use in inducing an immune response. For the reasons that follow, Applicants respectfully disagree.

C. Cited References Fail to Provide Requisite Motivation and Expectation of Success to Make or Use the *Specifically* Claimed Invention

A prima facie case of obviousness cannot stand without the Office "providing evidence of the motivating force which would impel one skilled in the art to do what the patent applicant has done" (*Ex parte Levengood*, 28 USPQ2d 1300, 1302 (Bd. Pat. App. & Inter. 1993) (emphasis added). Furthermore, "the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination" (see, e.g., MPEP2143.01 (emphasis in the original); see also *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)).

The Kedar article upon which the Office primarily relies, discusses only in very general terms compositions containing a tumor antigen and a cytokine for use in immunotherapy. The family of *cytokines*, however, is a large superfamily of molecules, of which *chemokines* are only a subgroup. The chemokines themselves are also a relatively large family, including nearly 50 members (see, e.g., abstract of Laing, K.J. and Secombes, C.J. (2004) Dev. Comp. Immunol. 28:443-60; copy enclosed). The current claims, however, are specifically directed to compositions that include the chemokines mC10 or vMCK-2. As noted above, these two specific chemokines were found to have significantly higher capacity to initiate infiltration of APCs than many other chemokines, some of which exhibited little or essentially no infiltration activity. The issue in this case thus becomes whether one of ordinary skill in the art in view of the cited art would have been impelled to select the particular combination of antigens and chemokines that are currently claimed.

This issue in the instant application is analogous to that raised in *Adams v. United States* (330 F.2d 622, 141 USPQ 361 (Ct. Cl. 1964). The Adams patent was directed to a nonrechargable battery that used a *magnesium* electropositive electrode and a *cuprous chloride*

electronegative electrode. Adams discovered that this particular combination of electrodes conferred several performance advantages. The U.S. government argued that batteries with zinc and silver chloride electrodes were known and that the prior art had suggested the substitution of magnesium for zinc to obtain a high voltage and substitution of cuprous chloride for silver chloride to achieve a constant current. These substitutions were said to yield the battery claimed by Adams.

In view of these facts, the court framed the issue as:

> [W]hether the fact that the individual constituents of the Adams battery have been long known in the art and have been used in various combinations in numerous batteries developed in the past, negates the essential element of novelty required in a valid patent, even though the specific combination used by Adams was never before disclosed and produced unusual and unexpected results. (*Id.* at 362).

The court concluded, that the Adams patent was valid because Adams had done more than select known elements with known properties to achieve a predictable result. The court stated:

> [T]he validity of the Adams patent is sustained on the ground that, in a crowded art, Adams selected *specific* components from the group of known battery components and found that the *combination* of these specific components resulted in a workable battery having unique and unexpected characteristics. (*Id.* at 364, emphasis in original).

The instant application is similar to the Adams case in that the current inventors have identified *specific* chemokines that can be used in combination with an antigen to yield a composition that has unexpectedly superior characteristics. Moreover, this superior performance is directly related to the goal the claimed invention seeks to achieve, namely an enhancement in

recruitment of APCs to the site of administration. This feature is important because the attraction of APCs to the region at which antigen is introduced (e.g., injection site) is believed to elicit a more robust reaction to the antigen included in the composition. Although not intending to be bound by any particular mechanism, and while the claims are patentable regardless of mechanism, it is thought that antigens are first taken up by the APCs and partially degraded. A fraction of the degraded antigen is subsequently displayed with MHC class I or II molecules on the surface of the antigen-presenting cells. Such cells can then in turn stimulate proliferation of T-cells, helper T-cells and/or the production of antibodies by B-cells (see, e.g., page 11, lines 24-29), thereby especially enhancing the adaptive immune response, which as noted above is important in, for example, in responses to cancer and viral, parasitic, yeast and fungal infections.

The results obtained with vMCK-2 and mC10 that are described in the instant application are unexpected, in part, because the cited references provide no basis for concluding that all cytokines, such as the chemokines discussed in this application, would vary widely in their effectiveness to induce chemotaxis and thus their utility in the antigen and cytokine compositions discussed in Kedar. Kedar, for instance, provides very little guidance on what particular cytokines could effectively be used in the cytokine and antigen compositions that are briefly discussed therein, thus leaving the impression that essentially any cytokine could be used in combination with an antigen in immunotherapy. The discussion in Mohamadzadeh, Orlofsky and Saederup regarding the involvement of mC10 and vMCK-2 in immune responses is also quite general and simply refers to chemotactic activities that are common to most chemokines (see, e.g., abstract from . There is thus nothing in these three references that would indicate that mC10 and vMCK-2 had activities that were distinct from any other chemokines. Hence, the overall view that emerges from these combined references is that essentially any cytokine (see, e.g., abstract from Laing, K.J. and Secombes, C.J. (2004) Dev. Comp. Immunol. 28:443-60; and abstract from Bernhard, M., et al. (2004) Trends in Immunology25:75-84; copies enclosed) could effectively be used in combination with an antigen to trigger infiltration of APCs to the site of injection and thus augment the immune response against the injected antigen.

But the *in vivo* results presented in the instant application demonstrate that there are significant differences even within the family of chemokines in their ability to exert a

chemotactic effect with respect to certain APCs. Examples 2-6, for example, provide *in vivo* comparative studies conducted with mice and rhesus monkeys that demonstrate that these two particular chemokines were significantly more effective at inducing chemotaxis of dendritic cells, mononuclear cells and polynuclear cells than a number of other chemokines. For instance, Tables 4, 5 and 6 (pages 62, 63-64 and 65, respectively) show that although several of the chemokines tested showed essentially no or minimal ability to induce chemotaxis of dendritic or mononuclear cells, whereas mC10 and MCK-2 showed significantly higher levels of activity. If this large variability exists within the chemokine family, presumably even larger variations in effectiveness would be expected in the larger cytokine superfamily discussed in Kedar.

Thus, the combined cited references simply provide a general description of a very large class of compositions that contain an antigen and cytokine, but they fail to provide the requisite guidance and motivation that would impel one of ordinary skill in the art to specifically select mC10 and vMCK-2 from the large family of *chemokines*, let alone the even larger superfamily of *cytokines* discussed in Kedar.

The results obtained with the currently claimed compositions are also unexpected because one of ordinary skill in the art could not have reasonably expected in view of the cited art that a *murine* chemokine (mC10) and a chemokine encoded by a *mouse* virus (vMCK-2) would nonetheless have the capacity to trigger migration of APCs in *primates* (see, e.g., specification at page 65, line 14-16; see also Examples 3-6), especially since there appears to be no human homolog of mC10 nor a homolog to vMCK-2 encoded by a virus that infects humans. All of the discussion in Mohamadzadeh, Orlofsky and Saederup focuses on results from murine model systems. There is no teaching or suggestion in the cited references that these chemokines would have activity in primates.

Thus, like Adams, the current inventors have done more than simply select known elements with known properties to achieve a predictable result. Rather, they found that chemokines varied significantly with respect to the desired activity and selected *specific* chemokines for use in combination with antigens that together have unique and unexpected characteristics. Accordingly, it is requested that this rejection should be withdrawn.

III. Amendments to Specification and Drawings

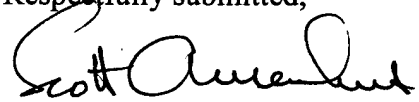
Formal drawings that comply with the requirements of 37 C.F.R. 1.84 are enclosed. Figure 1 has been amended as indicated in the attached annotated sheet to add text that was omitted from the drawings as filed. These additions add no new matter as this text was included in the figures submitted in parent application U.S. 09/834,814, which was incorporated by reference in its entirety.

The first paragraph of the application has been amended to: (1) indicate that the current application is a continuation-in-part of U.S. Application No. 09/834,814 and correctly list its filing date, (2) indicate that the current application is also a continuation-in-part of PCT Application PCT/US01/12162, and (3) indicate that U.S. Application No. 09/834,814 and PCT/US01/12162 both claim the benefit of U.S. Provisional Application No. 60/198,839, filed April 21, 2000.

A petition under 37 C.F.R. 1.78(a)(3) and the requisite fee has been submitted under separate cover to effectuate these changes. A copy of the petition is enclosed.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 303-571-4000.

Respectfully submitted,



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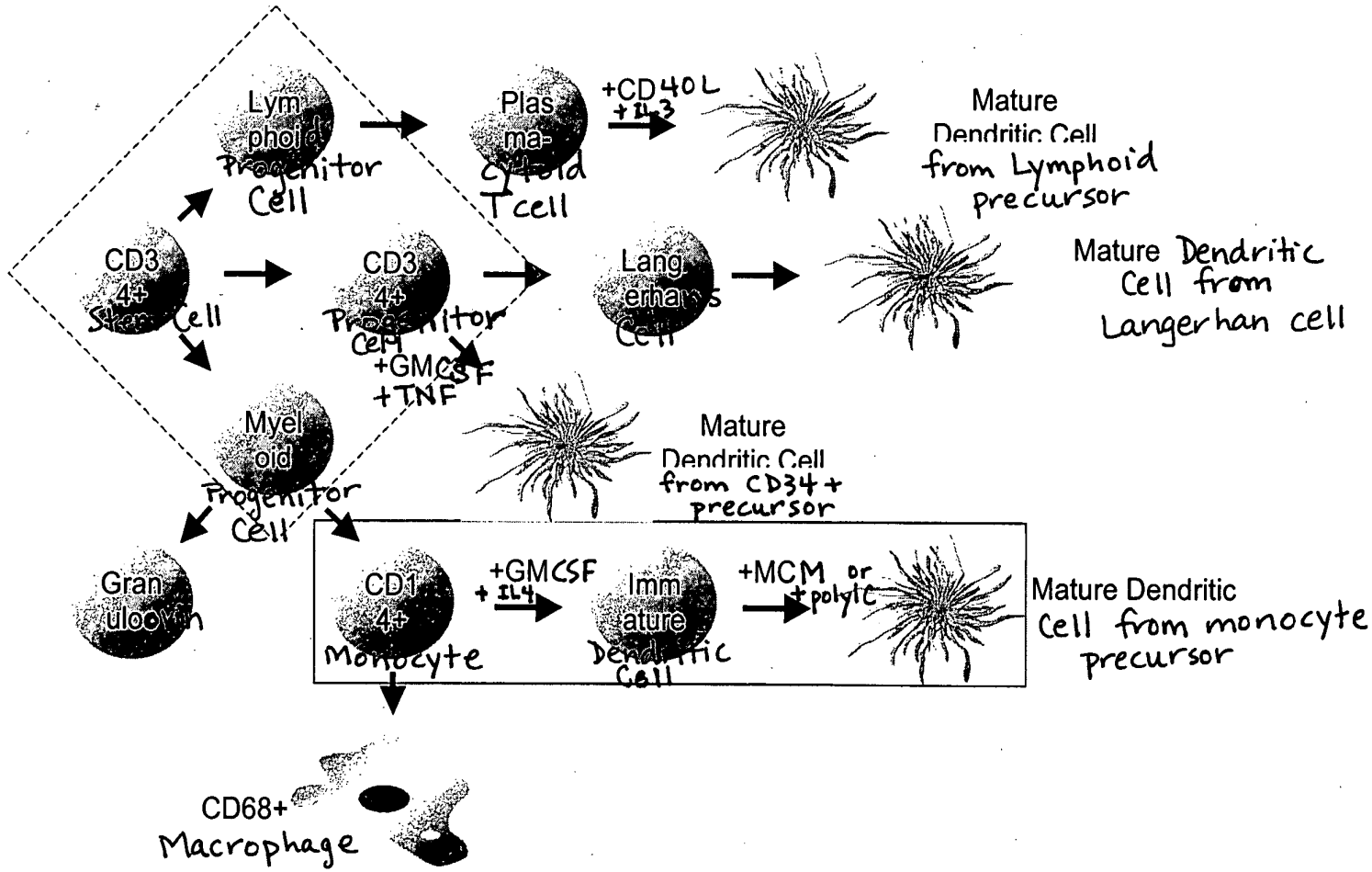

Annotated Sheet Showing Changes